Memory in biological regulatory circuits

Berichterstattung

Projektinformationen

YEASTMEMORY

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Projektwebsite

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Periodic Reporting for period 4 - YEASTMEMORY (Memory in biological regulatory circuits)

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Zusammenfassung vom Kontext und den Gesamtzielen des Projekts

Gene regulation allows cells to respond to internal and external stimuli and signals. Specifically, a certain trigger activates one or several molecular cascades that ultimately lead to an adaptation of the expression levels of certain genes. Naïvely, such regulation should always yield a similar response to

a given signal, unless changes in the organism's genetic information generate differences in the regulatory circuit.

However, this naïve view on gene regulation is now being challenged because recent observations suggest that a very rudimentary form of "memory" (i.e. the ability to store information about past experiences and use this information to adapt later behavior) may be rooted in regulatory circuits that exist even in relatively simple life forms like single-celled microbes. Advances in epigenetics have uncovered mechanisms that allow semi-stable non-genetic adaptations in the way that the genes of an organism are regulated. Moreover, recent developments in single-cell analyses have uncovered numerous examples of how genetically identical cells in the same environment do not always show the same response, and how a cell's response often depend on its history (referred to as "hysteresis", a technical term that indicates that a system's response depends on previous inputs or states). Specifically, microbes can adapt their response to a stimulus depending on past experiences, such as nutrients that were once available or stresses that were once present. Such history-dependent behavior might allow cells to prepare for future events that they have "learned" over evolutionary timescales to always expect after a priming event.

The traditional view of static and deterministic regulation is therefore gradually replaced by models with an important role for stochasticity (random or only partly regulated events) and hysteresis. Whereas the number of studies that report hysteresis steadily increasing, relatively little is known about the underlying mechanisms.

One the best-studied example of gene regulation is the regulation of switches between carbon sources in the budding yeast, Saccharomyces cerevisiae. When confronted with a mixture of different sugars, yeast cells first utilize glucose, before activating genes necessary for the consumption of non-preferred sugars like galactose or maltose (a phenomenon known as "catabolite repression"). The switch from glucose to non-preferred sugars takes some time (the so-called "lag phase") during which the cells stop consuming sugars and stop growing until they have activated the genes necessary to start the consumption of the alternative sugar. Interestingly, exposing yeast to maltose or galactose, then glucose, and then again maltose or galactose, reduces the average lag time. This implies that this regulation shows some form of "memory" or hysteresis.

OBJECTIVES AND SPECIFIC AIMS

Strategic objective

We propose a multidisciplinary approach to obtain a comprehensive view of the different genes and mechanisms that contribute to history-dependent behavior, and study its biological relevance.
To reach our goals, we will use the S. cerevisiae MAL circuit as a new model for hysteresis in gene regulation.

Specific scientific aims:

1. To provide a comprehensive description and quantitative analysis of hysteresis in MAL regulation (WP1)

2. To unravel the molecular mechanisms and genes contributing to hysteresis (WP2 and WP3)
3. To unravel the epigenetic mechanisms that allow hysteresis to extend over several generations (WP4)
4. To characterize the ecological relevance of hysteresis (WP5).

Specific Technological aims:
1. Development of new microfluidics devices that allow studying individual cell responses
2. Adaptation of the Chip-Exo technology to study nucleosome positioning using Illumina sequencing
3. Employ our knowledge to obtain superior industrial yeast variants with faster fermentation performance

Arbeit, die ab Beginn des Projekts bis zum Ende des durch den Bericht erfassten Berichtszeitraums geleistet wurde, und die wichtigsten bis dahin erzielten Ergebnisse

Overall, the project nicely followed the original plan.

We have characterized hysteresis in the MAL system in different conditions. Specifically, we confirmed strong hysteresis in MAL gene regulation that depends on the length of pre-growth in glucose. To do this, we used the commercially available microfluidics device produced by CellAsic, but we also developed and used our own microfluidics device in collaboration with the team of Prof. Peter Swain (Edinburgh U.) (WP1).

We have checked the effect of cell age and cell cycle on hysteresis and found that these factors do not have a significant effect (Scientific aim 2). In addition, we also performed the heterokaryon experiment described in WP2.2. Whereas this experiment proved to be technically challenging, we were able to get it to work and the results show that the hysteresis in MAL regulation is governed by a cytoplasmic factor (WP2).

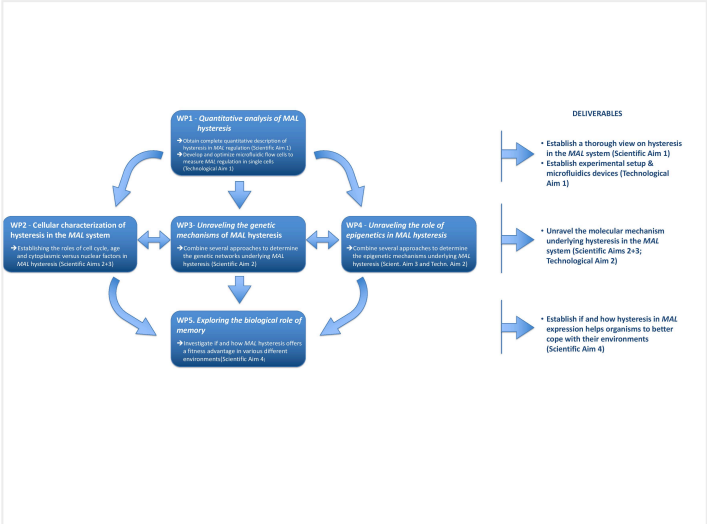
We have performed population-level RNAseq of cells that go through a transition from glucose to maltose (WP 3.1). The results show that the cells quickly repress genes involved in growth and then upregulate genes involved in respiration before activating the MAL genes needed to resume growth on maltose. We have also performed single-cell RNA-seq (which was indicated to be optional in the DoA), by adapting the standard protocol for the 10X Genomics platform to make this work for yeast cells. The results show that during the lag phase, cells need to activate respiration genes, and this happens at very different speeds in individual cells. The Bar-Seq experiment (WP 3.2) confirmed that genes involved in respiration, stress response and glucose repression play a pivotal role in controlling hysteresis in MAL gene regulation. In WP3.3 we identified an as-yet uncharacterized gene as a key regulator of the memory effect. We have filed a patent application for this discovery as we anticipate that the gene and alleles could be of commercial importance. IWe found that some naturally-occurring alleles of YLR108C are associated with a short lag and reduced memory, while other natural alleles give rise to longer lag phases and stronger memory. (Scientific Aim 2 + 3)

In WP5, we have investigated the eco-evolutionary tradeoffs of having a short- or long-lag allele of YLR108C. We found that deleting YLR108C, or having a short-lag allele, resulted in higher fitness in variable environments, while a long-lag allele yields an advantage in stable growth (Aim 5).

The main results so far of WP1-4 have been published in two papers in eLife, as well as in Current Genetics, mBio and Current Biology. We are preparing two additional papers that will be submitted in 2022. In addition, we have presented the results at various international conferences and workshops.

Fortschritte, die über den aktuellen Stand der Technik hinausgehen und voraussichtliche potenzielle Auswirkungen (einschließlich der bis dato erzielten sozioökonomischen Auswirkungen und weiter gefassten gesellschaftlichen Auswirkungen des Projekts)

Our results show that the current model for memory in cellular adaptation is wrong or at the very least not universal. Instead, we show that memory can involve broad and slow processes, eg a general shift in metabolic routing that simply takes a lot of time and energy for the cells to complete. In addition, we have shown that noise in growth rates has unexpected effects on fitness, with noise actually leading to an increase in fitness (for a given average growth rate). Lastly, our discovery of an as-yet uncharectrized gene, YLR108C, as a main regulator of lag behavior and metabolism in S. cerevisiae can be used to tune the industrial performance of yeast cells.



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